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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/822,161	03/30/2001	Michael Detmar	MGH 1512 CIP	6294

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EXAMINER	
DAVIS, NATALIE A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 12/04/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/822,161	Applicant(s) Detmar, et al.	
	Examiner Natalie A. Davis	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) *8-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claims 1-7, drawn to a method of treating a disorder by implanting a cell matrix disorder comprising cells that express a gene encoding an anti-angiogenic molecule, classified in class 514, subclass 44.

   II. Claims 8-15, drawn to a cell matrix structure, classified in class 424, subclass 93.1.

2. The inventions are distinct, each from the other because of the following reasons:

Inventions I (method) and II (product) are related as products and processes of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the method of Group I, VI may be used with a number of different products. The method of Group I may be practiced using various therapeutic agents. For example, the method may be practice by administering a gene encoding for angiostatin. The product of Groups II may be practiced using various methods and do not necessarily have to be used with the method of Group I. The cell matrix structure may be used to grow leukemia cells in vitro.

3. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, divergent subject matter, and require different search strategies, restriction for examination purposes as indicated is proper.

4. Applicant is advised that the response to this requirement, to be complete, must include an election of the invention to be examined even though the requirement be traversed.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one

or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

6. A voicemail message was left for Attorney Pabst on 4 November 2001 requiring an election to the restriction requirement as indicated above. A voicemail message was received from Attorney Pabst on 4 November 2001, wherein a provisional election was made with traverse to prosecute the invention of Group I, claims 1-7. Affirmation of this election must be made by applicant in replying to this Office action. Claims 8-15 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Priority

7. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application 60/127,221 upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 1-7 of this application. The claims are drawn to a method of treating a disorder comprising implanting a cell-matrix structure comprising cells, which express an anti-angiogenic molecule. The provisional application discloses thrombospondin -2 and uses thereof, which does not include a method of use comprising growing cells expressing thrombospondin -2 on a cell-matrix structure.***Claim Rejections - 35 USC § 112***

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 2 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating disorders characterized by excessive tissue proliferation, wherein the proliferation is due to angiogenesis, does not reasonably provide enablement for disorders characterized by excessive tissue proliferation, wherein the proliferation is not due to angiogenesis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claim is drawn to the method of claim 1 wherein the disorder is selected from the group consisting of malignant and benign neoplasias, vascular inflammatory conditions causing excessive proliferation of cells, keloid formation, intraperitoneal or inthrathoraic adhesions, endometriosis, congenital or endocrine abnormalities, psoriasis, unwanted skin proliferation, rheumatoid arthritis, multiple sclerosis, unwanted angiogenesis of the eye, restenosis, and infections causing excessive proliferation of the cells.

The nature of the invention is treatment of excessive proliferation using anti-angiogenic molecules. Hanahan, et al. (1996, Cell, 86:353-64) and Ferrara, et al., (Breast Cancer Res Treat, 1995, 36:127-37) are cited in order to in order to establish the general state of the art and level of predictability of treating cells characterized by excessive proliferation by administering an anti-angiogenic molecule. Hanahan, et al. disclose that in order for tumors to grow and metastasize, new blood vessels need to grow (angiogenesis). Ferrara, et al., set forth angiogenesis factor overexpression leads to enhanced tumor growth. There is no teaching in the art disclosing the use of an anti-angiogenesis molecule for the treatment of disorders, which are not induced by overexpression of angiogeneic factors. The art teaches tumor growth treatment using anti-angiogenesis molecules. The specification exemplifies tumor growth inhibition in mice using TSP-2, an angiogensis inhibitor (p. 32), but does not exemplify the treatment of a disorder characterized by excessive proliferation that was not due to the overexpression of angiogeneic factors. Since the prior art does not teach the treatment of disorders characterized by excessive proliferation, which are not due to angiogenesis and there is no guidance or exemplification in the specification showing the treatment of disorders using an anti-angiogenic factor, when angiogenesis is not the cause of the excessive growth, it would be unpredictable to practice the invention as claimed on disorders that are not due to angiogenesis. Accordingly, it would be unpredictable to one of ordinary skill in the art to use the method as claimed to treat disorders such as keloid formation, intraperitoneal or inthrathoraic adhesions, congenital or endocrine abnormalities, psoriasis, unwanted skin proliferation, rheumatoid arthritis, multiple sclerosis, restenosis, and infections causing excessive proliferation of the cells, since these disorders are not caused by angiogenesis.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vacanti, et al., (1988 and 5, 759830) in view of Locopo, et al., (1998) and Streit, et al, (1999).

10. The claims are drawn to method of treating a disorder characterized by excessive proliferation of the tissue comprising implanting a cell-matrix structure comprising cells, which express an anti-angiogenic molecule.

11. Vacanti, et al. teach a method of culturing cells (tissue specific cells) on a biodegradable, fibrous, polymer-cell scaffold and implanting the scaffold into animals. Vacanti, et al. further disclose successful engraftment, viability, mitotic figures and vascularization of cell masses. Vacanti, et al. teaches genetic engineering of cells for induction and repression of gene expression (col. 6), but does not teach to use cells expressing a gene encoding an anti-angiogenic molecule.

12. Locopo, et al. teach thrombospondin-1 as an endogenous angiogenesis inhibitor, which may be used to treat breast cancer, but does not teach the implantation of cells expressing thrombospondin-1 on a cell-matrix structure for the treatment of excessive proliferation.

13. Streit, et al, teach TSP-1 overexpression as an inhibitor of angiogenesis in cutaneous squamous cell carcinoma using stable tumor cell transfectants.

14. Since Vacanti, et al. teach successful implantation of cell-matrix structures comprising tissue specific cells on fibrous scaffolds in mammals and suggest that cells may engineered to express specific genes and Locopo, et al. teach thrombospondin-1 as an anti-angiogenic molecule, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to combine the teachings and

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implant cells engineered to express thrombospondin-1 on a cell-matrix structure for the treatment of excessive proliferation. One of ordinary skill in the art would have been motivated to combine the teachings because of the reasonable expectation of success based on well known and accepted methods in the art of how to use anti-angiogenic molecules to treat excessive proliferation and how to genetically engineer cells to produce anti-angiogenic molecules such as thrombospondin-1 as taught by Streit. Furthermore, one would be motivated to use the method to treat disorders caused by excessive proliferation because of the reasonable expectation of success that cells expressing the gene encoding thrombospondin-1 will grow on a polymer-cell scaffold and when implanted will inhibit angiogensis of any hyperproliferative cell. In addition, one would be motivated to substitute thrombomodulin for thrombospondin-1since both are known angiogenesis inhibitors.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Natalie A. Davis whose telephone number is 703-308-6410. The examiner can normally be reached on M-F 8-5:30 (every other Friday off).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4315 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Natalie A. Davis, Ph.D.
November 29, 2001

GEETHA P. BANSAL
PRIMARY EXAMINER